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Pearl Cohen Zedek Latzer, LLP
1500 Broadway
12th Floor
New York, NY 10036

EXAMINER
DEVI, SARVAMANGALA J N

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/089,583	PLESTED ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48,55,62-70,72-76 and 78-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48, 55, 62-70, 72-76 and 78-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendments

1) Acknowledgment is made of Applicants' amendments filed 05/12/08 and 01/11/08 in response to the non-final Office Action mailed 07/30/07.

Status of Claims

2) Claims 48, 55, 62-70, 72-76 and 78-81 have been amended via the amendment filed 05/12/08.

Claims 49, 56, 71 and 77 have been canceled via the amendment filed 05/12/08.

Claims 48, 55, 62-70, 72-76 and 78-81 are pending and are under examination.

Prior Citation of References

3) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Moot

4) The rejection of claims 49, 56, 71 and 77 made in paragraph 9 of the Office Action mailed 07/30/07 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claims.

5) The rejection of claims 49, 56, 71 and 77 made in paragraphs 10(a) and 10(h) of the Office Action mailed 07/30/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

7) The rejection of claim 71 made in paragraph 10(d) of the Office Action mailed 07/30/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

6) The rejection of claims 49, 56, 71 and 77 made in paragraph 11 of the Office Action mailed 07/30/07 under 35 U.S.C. § 102(b) as being anticipated by van der Ley *et al.* (*Mol. Microbiol.* 19: 1117-1125, 1996, already of record) as evidenced by Poolman JT (*Infectious Agent and Disease* 4: 13-28, 1995) and Vogel *et al.* (*Microbiol. Immunol.* 186: 159-166, October

1997) or van der Ley *et al.* (*Vaccine* 13: 401-407, 1995) (van der Ley *et al.,* 1995), is moot in light of Applicants' cancellation of the claims.

Rejection(s) Withdrawn

7) The rejection of claims 48, 55, 70 and 76 made in paragraph 10(b) of the Office Action mailed 07/30/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

8) The rejection of claim 48 made in paragraph 10(c) of the Office Action mailed 07/30/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

9) The rejection of claims 64, 65, 68, 69, 74 and 80 made in paragraph 10(f) of the Office Action mailed 07/30/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

Rejection(s) Maintained

10) The rejection of claims 48, 55, 62-70, 72-76 and 78-81 made in paragraph 9 of the Office Action mailed 07/30/07 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is maintained for the reasons set forth therein and herein below.

Applicants' arguments have been carefully considered, but are not persuasive for the reasons set forth below.

It is noted that Applicants have amended the independent claims to indicate that the recited immunogenic composition is substantially free from outer core lipopolysaccharide. Therefore, Applicants' arguments with regard to the issue of elicitation of an immune response in the presence of outer core LPS is moot. It is however noted that the source of the recited 'outer core lipopolysaccharide' is not specified in the claims, is not required to be *Neisseria* outer core lipopolysaccharide or *Neisseria meningitidis* outer core lipopolysaccharide.

Applicants contend that the subject specification described a conserved epitope, defined by the presence of PEtN at the 3-position of Hep2 of a *Neisseria* inner core LPS, and described that vaccines containing the conserved epitope elicit antibodies that recognize NM immunotypes L1, L3, L7, L8, L9, LI0, 1,11, and L12. Applicants point to the first paragraph of page 21 of the

specification and state that "recognize" and "'bind" are recognized in the art by synonyms in the context of raising antibody immune response and antibody recognition. Applicants state that the third full paragraph on page 6 of the specification describes that the epitope against which MAb B5 reacts has been characterized and can be used to form a vaccine to 'prevent *Neisseria* infections'. Applicants further state that the fourth paragraph of page 5 of the specification describes that the vaccine of the invention presents a conserved and accessible epitope that in turn promotes a functional and protective response. Applicants assert that the specification at third paragraph on page 28 described that MAb B5 is an lgG3 antibody which was raised against *Neisseria meningitidis* H44/76 immunotype L3; and that the specification at fourth paragraph of page 31 and second paragraph of page 33 respectively described the reactivity of MAb B5 with 76% of group B *Neisseria meningitidis* strains and with serogroups A, B, C, W, X, Y and Z. Applicants submit that this is conclusive data with respect to the efficacy of MAb B5 in possessing immuno-reactivity against the majority of naturally occurring, genetically diverse strains of *Neisseria meningitidis.* Applicants state that Table 2 on pages 41-42 of the specification demonstrates that MAb B5 is specifically reactive with L1, L3, L7, L8, L9, L10, L11 and L12 immunotypes.

However, contrary to Applicants' assertion, the third paragraph on page 28 of the specification as originally filed, describes that MAb B5 is an IgG3 antibody which was raised against *Neisseria meningitidis* H44/76 immunotype L3 ***galE***. The Office agrees with Applicants that MAb B5 recognizes L1, L3, L7, L8, L9, L10, L11 and L12 immunotypes of is an lgG3 antibody *Neisseria meningitidis*. However, as presented currently, *none of the instant claims* recite that the LPS inner core comprised in the recited immunogenic composition is a conserved LPS inner core and that it contains MAb B5-specific inner core epitope of *Neisseria meningitidis* H44/76 immunotype L3 ***galE***. The LPS inner core comprised in the immunogenic composition administered in the method of claims 48, 55, 62-64, 66-68, 70, 72-74, 76 and 78-80, as presented currently, is not limited to *Neisseria meningitidis* H44/76 immunotype L3 ***galE***.

Applicants submit that pages 25 and 26 of the instant specification describe the use of a rabbit polyclonal antibody specific for group B *Neisseria meningitidis* capsular polysaccharide obtained by immunizing a rabbit with lysates of MC58 with Freund's adjuvants and the pre-

adsorption of the polyclonal antibody with capsule-deficient mutant of MC58 to increase the specificity of the polyclonal antibody for the group B meningococcal capsular polysaccharide. However, the elicitation of a group B *Neisseria meningitidis* capsule-specific antibody by immunization of a rabbit with lysates of MC58 that contains a plethora of antigens is not relevant to the instantly claimed method, because the active immunogenic element in the instantly recited immunogenic composition is not a capsular polysaccharide of group B *Neisseria meningitidis*.

With regard to the Office's position that the infant rat model used in the passive protection experiment using an **avirulent** *galE* strain of *Neisseria meningitidis* as the challenging or infecting strain is of little prophylactic significant, Applicants submit the following arguments:

(a) Animal infection models are valuable for the development and preclinical assessment of meningococcal vaccines. It is only in animal models that interactions of the organism with the innate, humoral and cellular immune systems can be assessed.

(b) Infection of infant rats has been used to assess passive protection provided by sera raised against vaccine candidates or human vaccine sera. The specification of the present invention provides a valid recognized animal model that need not contain an example in human subjects, because the invention is disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation.

(c) The infant rat model is recognized as correlating to passive protection. The Office did not provide evidence that the model does not correlate.

However, whether or not infection of infant rats has been used to assess passive protection provided against a virulent strain of *Neisseria meningitidis* by sera raised against vaccine candidates or human vaccine sera is not the issue. The issue to be addressed is the use of an art-known avirulent strain of *galE* mutant strain of *Neisseria meningitidis* as the challenging/infecting strain in the infant rat model of passive protection. Contrary to Applicants' assertion, in paragraph 9 of the Office Action mailed 07/30/07, the Office set forth a detailed *prima facie* case of lack of enablement by establishing that the infant rat model used in passive protection against a *galE* strain of *Neisseria meningitidis* that has been demonstrated in the art to

be avirulent is of no prophylactic significance in a human or non-human host. That part of the Office's rejection is reproduced herein below:

> Furthermore, the limitation 'host' in the base claims encompasses a mammalian and a non-mammalian host, a human host including a human child, or a non-human host such as an infant rat. The phrase in the base claims 'antibody … capable of conferring passive protection against a *galE* mutant of an L3 immunotype of *Neisseria meningitidis* strain' leaves open the specific host(s) in whom the antibody is capable of conferring passive protection against a *galE* mutant of an L3 immunotype of *Neisseria meningitidis* strain. The conferring of passive protection against a *galE* mutant of an L3 immunotype of *Neisseria meningitidis* strain does not exclude but includes passive protection being conferred to a human host or an infant rat host against a *galE* mutant of an L3 immunotype of *Neisseria meningitidis.* The need for passive protection against any immunotype or strain of *Neisseria meningitidis* in a given host exists only if said immunotype or strain is virulent or pathogenic. The state of the art at the time of the instant invention documented that *galE* mutation dramatically alters the virulence potential of meningococci and that *galE* mutants of *Neisseria meningitidis* are "both serum sensitive and **avirulent** for infant rats", the avirulence being independent of encapsulation. See the first full sentence in left column on page 164 and the first two full sentences under 'Discussion' of Vogel *et al.* (*Microbiol. Immunol.* 186: 159-166, 1997) (Vogel *et al.*, 1997). Vogel *et al.* (1997) further discussed a previous study by Vogel *et al. Med. Microbiol. Immunol.* 185: 81-87, 1996 (Vogel *et al.*, 1996) on the meningococcal virulence in the infant rat model, which demonstrated that only the wild-type strains exhibited the capacity to spread systemically. See left column on page 160 of Vogel *et al.* (1997). The *galE* mutant of *Neisseria meningitidis* lacking the terminal three sugars of the LPS was shown to be avirulent despite the presence of a capsule, and was shown not to spread systemically into the blood stream even in animals infected with 10^8 CFU. No *galE Neisseria meningitidis* could be reisolated from the blood of even those animals that received a challenge dose of 10^8 CFU of *galE Neisseria meningitidis.* See paragraph bridging pages 85 and 86; paragraph bridging left and right columns on page 83; and right column of page 83; and Figure 1 of Vogel *et al.* (1996). The only hosts in which the only antibody, i.e., the monoclonal B5 antibody, that is evaluated in the instant specification for its ability to confer the supposed 'passive protection' against *galE* mutant of an L3 immunotype of *Neisseria meningitidis,* are infant rats. It should be noted that the challenge innoculum of the *galE* mutant of *Neisseria meningitidis* that Applicants used in their infant rat model is also 1 x 10^8 CFU (see the paragraph bridging pages 53 and 54 and the paragraph bridging pages 57 and 58 of the instant specification), a dose that is identical to the dose of 10^8 CFU of *galE Neisseria meningitidis* that is shown by Vogel *et al.* (1996) not to disseminate systemically in the infant rat model. Therefore, at least in infant rat hosts, the recited antibody cannot be characterized as having 'passive protective capacity' against *galE* mutant of an L3 immunotype of *Neisseria meningitidis.* An animal model of passive protection that uses an avirulent *Neisseria meningitidis* as the challenging or infecting strain is of little prophylactic significance in said animals. Furthermore, how this supposed passive protection in an avirulent infant rat animal model relates to or correlates with passive protection in a human adult or infant host against homologous *galE* mutant of an L3 immunotype of *Neisseria meningitidis*, or a heterologous virulent, invasive, wild type L3 immunotype of *Neisseria meningitidis,* is neither disclosed nor known. The rate of occurrence of *galE* mutants among naturally occurring carrier or clinical isolates of L3 immunotype *Neisseria meningitidis* is not known or disclosed.

Thus, the Office supported its rejection with the teachings from the art, i.e., teachings of Vogel *et al.* (*Microbiol. Immunol.* 186: 159-166, 1997) (Vogel *et al.*, 1997) and Vogel *et al. Med. Microbiol. Immunol.* 185: 81-87, 1996 (Vogel *et al.*, 1996). Applicants have provided no substantive arguments or evidence to show otherwise, let alone address the teachings of Vogel *et al.* (1997) and Vogel *et al.* (1996). An infant rat model that uses a **virulent** strain of *Neisseria meningitidis* is considered by those skilled in the art to be valuable for the development and

preclinical assessment of meningococcal vaccines. However, an infant rat model of passive protection that uses an art-established **avirulent** *galE* mutant strain of *Neisseria meningitidis* has not been correlated with passive protection in a human adult or human infant host within the instant specification or in the state of the art.

With regard to the issue of lack of enablement of inner core *Neisseria* LPS conjugates having the required function, Applicants point to the generic description on page 13 of the specification and state that this part of the specification describes that: (a) the 'immunogenic components' of the vaccine 'may be' conjugated to homologous or heterologous proteins; and (b) the 'immunogenic component of the present invention forms a saccharide peptide conjugate'. With this, Applicants conclude that the specification enables an 'immunogenic composition comprising an inner core of a *Neisseria* LPS conjugated to a protein or peptide'.

However, a mere statement in the specification that 'immunogenic components' of the vaccine 'may be' conjugated to a homologous or heterologous proteins; and that the 'immunogenic component of the present invention forms a saccharide peptide conjugate' is not sufficient to enable the claimed method which is required to elicit an antibody in a human or non-human host upon administration to said host an immunogenic composition comprises a first inner core of a Neisseria LPS conjugated to a protein or peptide, wherein the antibody elicited not is only required to bind to inner core LPS of *Neisseria meningitdis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, and but is also required to confer passive protection against a *galE* mutant of L3 immunotype of *Neisseria meningitdis*.

With regard to the Office's showing of lack of enablement of an inner core of a *Neisseria* LPS comprised in the recited immunogenic composition wherein the inner core is conjugated to a protein or peptide, wherein the conjugate composition is administered to a host to elicit an antibody that is not only required to bind to inner core LPS of *Neisseria meningitdis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, and but is also required to confer passive protection against a *galE* mutant of L3 immunotype of *Neisseria meningitdis*, Applicants submit the following arguments. Applicants contend that the disclosure in the present application was followed by successful results in Meningococcal conjugate vaccines containing four of the most common types of meningococcal bacteria. Applicants submit that the FDA has approved the

effective Quadrivalent Meningococcal Conjugate Vaccine (MCV4) and that a conjugate vaccine to meningococcal serogroup C is used for reducing the incidence of disease in young children in the UK. Applicants point to page 2 of the specification and state that the data provides support for the efficacy of this technology.

However, the approval by the FDA of a quadrivalent non-lipopolysaccharide conjugate vaccine, or the use of a serogroup C meningococcal non-lipopolysaccharide conjugate vaccine in the UK, is irrelevant to the instant rejection. These non-conserved, serogroup-specific, non-lipopolysaccharide conjugate vaccines have no meaningful nexus or relevance with the instantly claimed method which uses a conserved inner core *Neisseria* LPS that is serogroup non-specific, that is required, upon administration in a conjugate form, to elicit an antibody in a human or non-human host an antibody that (i) binds specifically to inner core of lipopolysaccharide of *Neisseria meningitdis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12; and (ii) is capable of conferring passive protection against a *galE* mutant of L3 immunotype of *Neisseria meningitdis*. The enabling disclosure and the evidentiary support have to come from the instant specification as filed. As set forth previously, the method claimed in the amended claims 64, 68, 74 and 80 used an immunogenic composition comprising an inner core of a *Neisseria* LPS of the recited structure being conjugated to a protein or peptide. However, a method of eliciting an antibody that binds to an inner core LPS of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, and that is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain comprising administering a formalin-killed, outer core-lacking *galE* mutant whole cells of *Neisseria meningitidis* H44/76 strain as disclosed in the instant specification does not enable a method of eliciting an antibody that binds to an inner core LPS of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, and is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain comprising administering an immunogenic composition comprising an inner core of any *Neisseria* LPS wherein said inner core, substantially free of outer core LPS of said *Neisseria*, is conjugated to a protein or peptide. The process of conjugation of a conserved inner core LPS to a protein or peptide can block the conserved, serogroup-nonspecific inner core epitope or the protective inner core epitope, can alter the conformational integrity of the inner

core, and/or can modify the chemical structure of the inner core. With regard to the immunogenicity of inner core LPS *conjugates* and their ability to induce functional antibodies, page 35 of the instant specification states the following [Emphasis added]:

> **Future studies will look at** the safety and immunogenicity of inner core LPS-conjugates (PEtn at 3-position of HepII and alternative glycoforms) and the functional ability of the polyclonal antibodies in opsonic and serum bacterial assays, initially in mice and rabbits.

The law with regard to the unpredictability factor is clear. The predictability or unpredictability is a *Wands* factor. MPEP 2164.03 [R-2] sets forth the relationship of predictability of the art and the enablement requirement. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The 'amount of guidance or direction' refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004). The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of a method of administering a formalin-killed, outer core-

lacking *galE* mutant whole cells of *Neisseria meningitidis* H44/76 strain as disclosed in the instant specification will extrapolate to a method of eliciting an antibody that binds to an inner core LPS of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, and is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain comprising administering an immunogenic composition comprising an inner core of any *Neisseria* LPS wherein said inner core, substantially free of outer core LPS of said *Neisseria*, is conjugated to a protein or peptide. The instant specification itself at paragraph bridging pages 34 and 35 acknowledges the art known unpredictability in eliciting functional (bactericidal) antibodies by a conjugate of an *N. meningitidis* immunoype inner core oligosaccharide as reflected in the study carried out by (Verheul, A.F., *et al.* 1991. *Infect Immtm.*59: 843-851). The lack of guidance within the instant specification when taken in combination with the unpredictability factor raises the need to engage in considerable undue experimentation. The courts have held that it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement. See *Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001).* Moreover, the specification must have been enabling at the time the invention was made (see *In re Wright, 27 USPQ2d 1510*). A claim must be enabled over its whole breadth. The rejection stands.

11) The rejection of claims 48, 55, 70 and 76 made in paragraph 10(a) of the Office Action mailed 07/30/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for the reasons set forth therein and herein below.

Applicants state that they disagree with the rejection and that they have amended claims 48 and 55 to expedite prosecution. Other than this, Applicants have not advanced any substantive arguments to explain why they disagree. As set forth previously, not only claims 48 and 55, but also claims 70 and 76, continue to include the indefinite, incorrect and/or confusing limitations 'position 3 of a HepII moiety of said inner core' and 'an inner core LPS'. The limitations 'a HepII moiety of said inner core' and 'an inner core LPS' convey that the recited *Neisseria* LPS has more than one HepII moiety in the inner core and more than one inner core in the LPS. However, all through the specification, the application describes the *Neisseria* LPS to have no

more than one inner core and no more than one HepII moiety. See pages 7 and 8 of the instant specification for example, which include the recitations: 'the 3-position of HepII' and 'the inner core … of *Neisseria meningitidis* LPS'. To obviate the rejection, it is suggested that Applicants replace the limitation 'a HepII moiety' with the limitation --HepII moiety-- and the limitation 'a ….. inner core' with --the inner core--.

12) The rejection of claims 62, 66 and 78 made in paragraph 10(d) of the Office Action mailed 07/30/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for part of the reasons set forth therein and herein below.

Applicants state that they disagree with the rejection and that they have amended claims 62, 66 and 78 to expedite prosecution. Applicants have amended the claims to specify the source of the recited outer core. However, the claims continue to include the limitation 'a presence of an outer core LPS'. Since the specification indicates the presence of no more than one outer core in the LPS of *Neisseria meningitidis* immunotypes L1, L3 and L7 to L12, it is suggested that Applicants replace the above-identified limitation with the limitation --the presence of outer core LPS--.

13) The rejection of claims 63, 67, 73 and 79 made in paragraph 10(e) of the Office Action mailed 07/30/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for part of the reasons set forth therein and herein below.

Applicants state that they disagree with the rejection and that they have the amended claims to expedite prosecution. Applicants have amended the claims to specify the source of the recited bacterial capsule. However, the claims continue to include the limitation 'a presence of a bacterial capsule of ….'. Since the specification indicates the presence of no more than one capsule in *Neisseria meningitidis* immunotypes L1, L3 and L7 to L12, it is suggested that Applicants replace the above-identified limitation with the limitation --the presence of capsule--.

14) The rejection of claims 75 and 81 made in paragraph 10(f) of the Office Action mailed 07/30/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for the reasons set forth therein and herein below.

Applicants state that they disagree with the rejection and that they have the amended claims to expedite prosecution. However, while amendments have been made to claims 64, 65,

68, 69, 74 and 80, claims 75 and 81 continue to include the limitation: 'a *Neisseria* LPS'. The rejection stands.

15) The rejection of claims 48, 55, 70 and 76 made in paragraph 10(g) of the Office Action mailed 07/30/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for the reasons set forth therein and herein below.

Applicants state that they provided an infant rat model, considered by those skilled in the art, valuable for the development and preclinical assessment of meningococcal vaccines. Applicants maintain that the infant rat model provides valuable, clear, *in vivo* information concerning the interactions of the vaccine with the innate, humoral and cellular immune systems. Applicants assert that infection of infant rats for assessing passive protection has been described in such detail that the claim limitation of claims 48, 55, 70 and 76 is definite.

Applicants' arguments have been carefully considered, but are not persuasive. Instant claims continue to include the limitation: 'capable of conferring passive protection against a galE mutant of an L3 immunotype *Neisseria meningitidis* strain' without specifying in whom the recited antibody is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain. Contrary to Applicants' argument, the claims do not recite that the antibody is capable of conferring passive protection in infant rats against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain. Furthermore, as presented currently, the limitation identified above is vague and repugnant because the art recognizes *galE* mutant of *Neisseria meningitidis* to be an avirulent or non-pathogenic strain that does not require or necessitate passive protection. As set forth previously, the state of the art recognizes that *galE* mutation dramatically alters the virulence potential of meningococci and that *galE* mutants of *Neisseria meningitidis* are "both serum sensitive and **avirulent** for infant rats", the avirulence being independent of encapsulation. See the first full sentence in left column on page 164 and the first two full sentences under 'Discussion' of Vogel *et al*. (*Microbiol. Immunol*. 186: 159-166, 1997) (Vogel *et al*., 1997, already of record). The rejection stands.

16) The rejection of claims 62-69, 72-75 and 78-81 made in paragraph 10(h) of the Office Action mailed 07/30/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for the reasons set forth therein.

17) The rejection of claims 48, 55, 62-70, 72-76 and 78-81 made in paragraph 11 of the Office Action mailed 07/30/07 under 35 U.S.C § 102(b) as being anticipated by van der Ley *et al.* (*Mol. Microbiol.* 19: 1117-1125, 1996, already of record) as evidenced by Poolman JT (*Infectious Agent and Disease* 4: 13-28, 1995, already of record) and Vogel *et al.* (*Microbiol. Immunol.* 186: 159-166, October 1997, already of record) or van der Ley *et al.* (*Vaccine* 13: 401-407, 1995, already of record) (van der Ley *et al.,* 1995), is maintained for the reasons set forth therein and herein below.

Applicants assert that the system described by van der Ley *et al.* is materially different from the claims of the subject application, and that van der Ley *et al.* does not qualify as a 102 reference. Applicants contend that the experiments performed by van der Ley *et al.* do not include elicitation of antibodies, but are limited to the basic ability of certain monoclonal antibodies to screen for engineered strains of *Neisseria meningitidis* that are defective in LPS biosynthesis. Applicants state that the monoclonal antibodies used by van der Ley *et al.* were initially raised after immunization with outer membrane complexes (OMCs) whereas the claims of the present application are directed at eliciting in a host an antibody that specifically binds to an inner core of lipopolysaccharide by administering to a host an immunogenic composition comprising an inner core of a *Neisseria* lipopolysaccharide (LPS) substantially free from outer core lipopolysaccharide. Applicants allege that the Office has erred in asserting that the methods disclosed by van der Ley *et al.* include immunizing experimental animals by administering immunogenic meningococcal *galE* mutant LPS that elicited antibodies recognizing novel epitopes in the inner-core region and that one of the antibodies thus elicited binds to the *galE* mutant and wild-type strains. Applicants assert that the present application at page 21 provides that the designated MAb B5 was obtained by immunizing mice with a *galE* mutant of *Neisseria meningitidis* H44/76 (B.I5.P. 1.7.16 immunotype L3). Applicants further submit that the HC-L3 and ES-L3 strains of van der Ley *et al.* are stable L3 negative mutants containing an erythromycin resistance marker. These strains are different from the strains described in the present application which are not erythromycin resistant strains and/or stable L3 negative mutants. Applicants point to Figure 1 and contend that testing of MAbs of the present application was carried out by screening against purified LPS from *Neisseria meningitidis* L3, and *Salmonella typhimurium* Ra

and Re mutants. Applicants assert that the amended claims 48, 55, 70, and 76 include administering to a host an immunogenic composition comprising an 'inner core of' a *Neisseria* lipopolysaccharide (LPS) substantially free from outer core lipopolysaccharide, and that van der Ley's LPS-containing outer membrane complex immunogen preparation from a *galE* mutant of strain H44/76 (L3 immunotype) of *Neisseria meningitidis* administered to experimental animals is entirely different from the *Neisseria mneningitidis* strain of the present invention derived from the *galE* mutant of the H44/76 strain. Applicants state that in relying upon the theory of inherency, the Office must provide a basis and technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the disclosure of the applied prior art. Applicants cite MPEP 2112 and argue that the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish inherency or that result or characteristic. Applicants further argue that inherency may not be established by probabilities or possibilities and that the Office failed to meet its burden of proving inherent anticipation in van der Ley *et al.* with respect to a phosphoethanolamine moiety linked to position 3 of HepII moiety. Applicants assert that Vogel *et al.*, Poolman *et al.*, van der Ley *et al.* (1995), and van der Ley *et al.* (1996) provide no data disclosing or suggesting elicitation of antibodies against *galE* mutant of an L3 immunotype of *Neisseria meningitidis* strain as recited in the amended claims. Applicants conclude that van der Ley *et al.* (1996) neither discloses nor suggests the subject matter of the subject claims.

Applicants' arguments have been carefully considered, but are not persuasive. As set forth previously, it is noted that the instant specification identifies H44/76 strain of *Neisseria meningitidis* as an L3 immunotype strain. It is well known that *galE* mutant lacks outer core structures. See the specification on page 6; see the Table on page 36, and first paragraph on page 47. It is further noted that the inner core of a *Neisseria* LPS comprised in the recited immunogenic composition is not required to be from a *galE Neisseria* mutant.

As set forth previously, van der Ley *et al.* taught a method of immunizing experimental animals by administering immunogenic meningococcal *galE* mutant LPS that elicited antibodies recognizing novel epitopes in the inner-core region. One of the antibodies thus elicited binds to the *galE* mutant *and* wild-type strains. van der Ley *et al.* also taught a method of immunizing

experimental host animals with an outer membrane complex preparation from a *galE* mutant of strain H44/76 (L3 immunotype) of *Neisseria meningitidis* mixed in an adjuvant, and the selection of positive hybridomas using *galE* LPS as the coating antigen in ELISA. See paragraph bridging pages 1122 and 1123; and last full paragraph on page 1123. Thus, contrary to Applicants' assertion, the experiments performed by van der Ley *et al.* do include elicitation of antibodies. The last full paragraph on page 1123 of van der Ley *et al.* expressly taught the following [Emphasis added]:

> Four new **mAbs directed against *galE* mutant LPS**, i.e. MN31A4.31, MN31D8.51, MN31E8.41 and MN31G9.19, **were isolated after immunization with outer membrane complexes (OMCs) from a *galE* mutant derivative of strain H44/76. .... Positive hybridomas were selected using ELISA with *galE* LPS as the coat antigen.**

The paragraph bridging pages 1122 and 1123 of van der Ley *et al.* expressly taught the following [Emphasis added]:

> ..... mAbs have ... been isolated **after immunization with *galE* LPS.** .... one of the four **new mAbs also binds ..... to the LPS of the *galE* mutant and wild-type strains.** These results show that by using mutant LPS, structures in the inner core, which are not normally immunogenic, can now become so. When also accessible in wild-type strains, such epitopes could be valuable for vaccine purposes, because the inner core is more conserved among different strains and is not known to contain host-identical epitopes.....

Clearly, the prior art LPS-containing immunogen administered to experimental animals is derived from the *galE* mutant of the same identical H44/76 strain of *Neisseria meningitidis* that is used by Applicants to generate MAb B5 specific to the neisserial inner core LPS. Since the prior art immunogenic inner core-containing *galE* mutant LPS or the prior art inner core-containing outer membrane complex preparation from the *galE* mutant of strain H44/76 of *Neisseria meningitidis* are not fully purified, they are expected to comprise a contaminant protein or peptide naturally conjugated thereto. That the prior art LPS-containing immunogen derived from the *galE* mutant of the same identical H44/76 strain of *Neisseria meningitidis* as that used by Applicants comprises a phosphoethanolamine moiety linked to position 3 of HepII moiety is inherent from the teachings of van der Ley *et al.* in light of what is well known in the art. For instance, Poolman JT disclosed of the existence of phosphoethanolamine moiety linked to position 3 of Hep2 moiety of the inner core of the lipopolysaccharide of native and *galE* immunotype L3 of *Neisseria meningitidis.* See Figure 2. That the prior art LPS-containing immunogen derived from the *galE* mutant of lacks an outer core in the LPS is also inherent from

the teachings of the prior art in light of what is known in the art. For instance, Vogel *et al.* showed that *galE* mutation results in a truncated LPS that lacks the outer core (see Figure 1). Similarly, van der Ley *et al.* (1995) taught that *galE* deletion in *Neisseria meningitidis* leads to the synthesis of galactose-deficient LPS in addition to teaching the desirability of lack of lacto-N-neotetraose structure in a *galE* vaccine strain (see paragraph bridging page 403). Therefore, the prior art method necessarily elicits an antibody that has the intrinsic ability to recognize *Neisseria meningitidis* immunotypes L1, L3 and L7-L12 in the presence or absence of an outer core LPS, and the intrinsic capability of conferring passive protection against a *galE* mutant of an *Neisseria meningitidis* L3 immunotype strain. The accessibility to the recited antibody in the presence of a capsule of *Neisseria meningitidis* is not a property of the recited antibody, but is an intrinsic property of the inner core LPS of the recited immunotypes or naturally occurring strains of *Neisseria meningitidis*. The prior art method, which elicits antibodies both to the *galE* mutant *and* wild-type strains of *Neisseria meningitidis* is expected to necessarily immunize the murine host against 'a majority' of naturally occurring strains of *Neisseria meningitidis* in light of what was known in the art at the time of the invention. For instance, Poolman taught that L3 immunotypes alone account about 80% of (i.e., majority of) meningococcal isolates from group B cases. See Figure 3 of Poolman.

The Office's position that van der Ley's method is the same as the Applicants' method is based upon the fact that the prior art method uses the inner core-containing immunogen composition from the same L3 immunotype H44/76 strain of *N. meningitidis* as the one used by Applicants in the instant specification. Therefore, the prior art inner core-containing immunogen is expected to necessarily have the same intrinsic structure and the same immunogenic, protective, and/or cross-reactive properties as that of the Applicants' immunogenic composition. Since the Office does not have the facilities for examining and comparing Applicants' method with that of the prior art method, the burden is on Applicants to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the prior art method does not induce the same functional effects as the claimed method). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

Claims 48, 55, 62-70, 72-76 and 78-81 are anticipated by van der Ley *et al.* The reference of Poolman, Vogel *et al.* (1997) or van der Ley *et al.* (1995) is **not** used as a secondary

reference in combination with van der Ley *et al*., but rather is used to show that every element of the claimed subject matter is disclosed by van der Ley *et al*. with the unrecited characteristics being inherent therefrom. See *In re Samour* 197 USPQ (CCPA 1978). Contrary to Applicants' assertion, Vogel *et al*., Poolman *et al*., van der Ley *et al*. (1995) and van der Ley *et al*. (1996) were not cited in the rejection as providing data disclosing or suggesting elicitation of antibodies against *galE* mutant of an L3 immunotype of *Neisseria meningitidis* strain as recited in the amended claims, but to show that every element of the claimed subject matter is disclosed by van der Ley *et al*. with the unrecited characteristics being inherent therefrom.

'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co*., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc*., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). Also note that the critical date of extrinsic evidence showing a universal fact need **not** antedate the filing date. See MPEP 2124. Thus, contrary to Applicants' allegation, the Office has provided the basis and sufficient technical reasoning to reasonably support the determination that the inherent characteristics necessarily flow from the disclosure of the applied prior art.

With regard to Applicants' arguments, whether or not HC-L3 and ES-L3 strains of van der Ley *et al*. are stable L3 negative mutants containing an erythromycin resistance marker, is irrelevant. What is relevant is that the *galE* mutant of strain H44/76 (L3 immunotype) of *Neisseria meningitidis* used by van der Ley *et al*. and the *galE* inner core-containing immunogenic composition therefrom are the same as the ones used by Applicants. With regard to Applicants' argument that MAb B5 was obtained by immunizing mice with a *galE* mutant of *Neisseria meningitidis* H44/76 (B.I5.P. 1.7.16 immunotype L3), it should be noted that 'MAb B5' is not claim limitation currently. The generic limitation 'antibody' in the instant base claims encompasses a polyclonal antibody, and a monoclonal antibody other than MAb B5. With regard

to Applicants' argument that monoclonal antibodies used by van der Ley *et al.* were initially raised after immunization with outer membrane complexes (OMCs) whereas the claims of the present application are directed at eliciting in a host an antibody that specifically binds to an inner core of lipopolysaccharide by administering to a host an immunogenic composition comprising an inner core of a *Neisseria* lipopolysaccharide (LPS) substantially free from outer core lipopolysaccharide, the following must be noted. The limitation in the instant base claims 'immunogenic composition comprising' represents open claim language. The transitional term 'comprising' is synonymous with 'including', 'containing', or 'characterized by' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; and *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ('comprising leaves 'the claim open for the inclusion of unspecified ingredients even in major amounts'). Furthermore, the recited 'a first inner core of a Neisseria lipopolysaccharide' is not required to be purified, not even required to be isolated, and therefore encompasses inner core LPS naturally present in association with van der Ley's immunogenic OMPC from *galE* mutant of *Neisseria meningitidis* H44/76 (B.I5.P. 1.7.16 immunotype L3). The inner core LPS lacking outer core LPS is 'comprised' within van der Ley's immunizing composition that comprises OMPC from *galE* mutant of *Neisseria meningitidis* H44/76 (B.I5.P. 1.7.16 immunotype L3). As recited currently, the presence of the prior art OMPC from *galE* mutant of *Neisseria meningitidis* H44/76 (B.I5.P. 1.7.16 immunotype L3) is not excluded from the immunogenic composition of the instant claims. For the reasons delineated above, the teachings of van der Ley *et al.* anticipate the instant claims. The rejection stands.

New Rejection(s) Necessitated by Applicants' Amendment

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

18) Claims 48, 55, 62-70, 72-76 and 78-81 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 48, 55, 70 and 76, as amended, include the new limitation: 'a first inner core of a *Neisseria* lipopolysaccharide'. Claims 70 and 76, as amended, include the new limitations: 'a second' inner core LPS of a majority of naturally occurring strains of *Neisseria meningitidis.* Claims 48 and 55, as amended, include the new limitations: 'a second inner core of lipopolysaccharide of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12'. Claims 62, 63, 66, 67, 72, 73, 78 and 79 include the new limitation: 'said second' inner core. Claims 64, 65, 68, 69, 74, 75, 80 and 81 include the new limitation: 'said first' inner core. The limitation 'a first inner core of a *Neisseria* lipopolysaccharide' implies that a *Neisseria* lipopolysaccharide has a first, a second, a third etc. inner cores. Similarly, the limitation 'a second' inner core LPS of a majority of naturally occurring strains of *Neisseria meningitidis* implies that a majority of naturally occurring strains of *Neisseria meningitidis* contain a first, a second, a third etc. inner cores. The limitation 'a second inner core of lipopolysaccharide of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12' implies that lipopolysaccharide of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12 contains a first, a second, a third etc. inner cores. However, there is no descriptive support in the instant specification for such limitations. Applicants have not pointed o specific parts of the specification that support these new limitations and the now claimed new scope of the claims. A *Neisseria* LPS or a lipopolysaccharide of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12 comprising therein more than one inner core is not supported in the instant specification, as originally filed. Therefore, the above-identified limitation(s) in the claims and the current scope of the claims constitute new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed by pointing to specific lines and pages, for the new limitations, or alternatively, remove the new matter from the claim(s). Applicants should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

19) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

20) Claims 48, 55, 62-70, 72-76 and 78-81 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 48, 55, 70 and 76, as amended, are indefinite in the limitation: 'composition comprising a first inner core of a Neisseria lipopolysaccharide (LPS) **and** is substantially free from outer core lipopolysaccharide' [Emphasis added], because it is unclear whether it is the immunogenic composition that is substantially free from outer core lipopolysaccharide, or whether it is the recited inner core that is substantially free from outer core lipopolysaccharide. If the latter is intended, it is suggested that Applicants replace the limitation 'and' with the limitation --which is--.

(b) Claims 48, 55, 70 and 76, as amended, are indefinite in the limitation: 'composition comprising a first inner core …… and substantially free from outer core lipopolysaccharide'. The term 'substantially free' is a relative term which is not specifically defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the claim. What amount, length, or element of the recited outer core lipopolysaccharide has to be absent in the recited composition such that the composition qualifies as a composition that is 'substantially free from outer core lipopolysaccharide' is unclear.

(c) Claims 63, 67, 73 and 79, as amended, are indefinite because these claims lack proper antecedent basis in the limitation: 'bacterial capsule of a *Neisseria meningitidis* strain'. These claims depend from claims 48, 55, 70 and 76 respectively, which recite '*Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12'. For proper antecedence, and to be similar to the correction/amendment made to claims 62, 66, 72 and 78, it is suggested that Applicants replace the above-identified limitation with the limitation: --capsule of said *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12--.

(d) Claims 55, 62-70, 72-76 and 78-81, which depend directly or indirectly from claims 48, 55, 70 and 76, are also rejected as being indefinite because of the indefiniteness identified above in the base claims.

Remarks

21) Claims 48, 55, 62-70, 72-76 and 78-81 stand rejected.

To be consistent with the claim language used in claims 48, 55 and 70, it is suggested that Applicants replace the limitation 'whereby' in claims 55 and 76 with the limitation --wherein--.

To be consistent with the italicized limitation '*galE*' used all through the instant specification and in the art, it is suggested that Applicants replace the non-italicized limitation 'galE' in the instant claims with the italicized limitation --*galE*--.

22) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

23) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted to the Office' Central Rightfax number 571-273-8300 via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week.

24) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

25) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Acting supervisor, Shanon Foley, can be reached at (571) 272-0898, or Robert Mondesi, can be reached at (571) 272-0956.

/S. Devi/
S. Devi, Ph.D.
Primary Examiner
AU 1645

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